REMARKS

The above amendments are in response to the Office Action dated August 31, 2010. Paragraph [0072] of the specification and claims 1, 7 and 16 are amended. Support for the amendment to paragraph [0072] can be found in claim 10 as originally filed. Support for the amendment to claim 1 to recited "fast, temporary relief of pain" can be found, *inter alia*, in paragraph [0007]. The amendment to claim 7 simply removes the word "the". No new matter is added with this amendment.

I. Objections to the Specification

The specification as previously amended is objected to because, according to the Examiner, "FA" could mean "Fatty Acid" or "Fatty Alcohol". In response, Applicants have amended paragraph [0072] to indicate that FA is either fatty acid or fatty alcohol, as the Examiner has pointed out with reference to original claim 10. Applicants believe the amendment is sufficient to define these abbreviations wherever they appear.

II. Double Patenting.

Claims 1-9, 12, 14 and 16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of copending Application No. 12/212,093. Applicants will fully respond to this provisional rejection upon notification of allowable subject matter.

III. Claim Rejections – 35 USC § 112

Claims 1-3, 6, 12, 14 and 16 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner states in paragraph 9 that there is no indication in the specification as originally filed that substituents X and Y are optional. The Examiner also objects to claim 2, for reciting different monomers. In response, applicants have amended claim 1 and have deleted claim 2, without prejudice or disclaimer. This rejection is therefore rendered moot with this amendment.

The Examiner also objects to the recitation of treating pain but not "the condition that causes the pain" arguing that this is new matter. According to the Examiner, the specification as originally filed indicates that the polymers are not intended to treat the various different lesions causing the pain or itching and that such disclosure does not support the broad limitation of the amended claims. Applicants respectfully traverse this rejection.

Applicants herewith amend claim 1 to further clarify that the pain treatment of the present invention involves fast, temporary relief of pain. Support for this clarification can be found in paragraphs [0007] and [0058], where applicants describe relief of pain, within minutes of administration of the claimed compounds, which lasted a few hours to a few days. It is also clear from this amendment and paragraph [0058] that the purpose of the claimed invention is not to treat the underlying disease or disorder that causes the pain. In view of this amendment, applicants respectfully request the Examiner to reconsider the objections to the scope of applicants' claims. Applicants' reliance upon

an example depicting the treatment of pain associated with a lesion is simply one example of the efficacy of the invention and should not be construed as limiting the invention in any way. Under US law, it is not necessary for an applicant to provide examples of each embodiment covered by the claims. Likewise, although applicants may have described instances where the cause of the pain was also treated e.g., paragraphs [0054] and [0055], applicants are not claiming this embodiment. Applicants are claiming a treatment of pain that is fast and temporary. In view of the above amendment and explanations, applicants respectfully request the Examiner to withdraw this rejection.

The Examiner also rejects claims 1-3, 6 and 12-16 for lack of written description. According to the Examiner, the application fails to describe the amount of biocompatible polymer that treats pain but results in a method not treating the condition that causes the pain and how those amounts might vary. In response, applicants again point out that claim 1 has been amended to recite that pain relief is fast and temporary. Applicants provide numerous examples in the specification (*e.g.,* paragraphs [0092][0097][0120][0125][0143][0154][0158][00181]) where solutions containing an amount of the claimed polymer caused fast and temporary relief of pain. Applicants agree that the amount of the polymer may vary depending upon the formulation and specific subject. However, ascertaining such amounts calls only for routine experimentation. In view of the amendment to claim 1 and these comments, applicants respectfully request the Examiner to reconsider and withdraw this rejection.

Claims 1-3, 6 and 12-16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner states that because dependent claims 12-16 recite various causes of pain, it is unclear at what level an underlying condition is or is not being treated. For instance, the examiner refers to claim 16, which recites peripheral and/or degenerative neuropathy. The Examiner asks whether in diabetic neuropathy the underlying condition is being treated. Applicants understand the Examiner's position to be that when the definition of the disorder itself is a type of pain, then applicants' invention inherently treats the condition. In response, applicants wish to

clarify that neuropathies, such as diabetic neuropathy and Parkinson Disease or Multiple Sclerosis - related neuropathy are progressive diseases caused by degeneration at the nerve endings. In the case of diabetes, the diabetes increases microthrombosis, which induces suffering by the lack of oxygen in tissues, generally, and in nerves, specifically. The nerve endings progressively degenerate (neuropathy) (Example 4). Applicants' intention is to include within the scope of the invention any pain associated with neuropathies related to diabetes or any other disease. The biopolymers of the invention treat the pain, not the diabetes or other underlying disease that is caused by diabetes (*i.e.* degenerative nerve endings). Applicants also point out that claim 16 depends from amended claim and therefore incorporates the recitations in claim 1. With regard to the Examiner's concern about scars, Applicants believe there is a clear distinction between a scar and pain associated with such scar. In further response, applicants again direct the Examiner's attention to the amendment to claim 1, where the treatment is fast and temporary. As such, applicants do not intend to claim remodeling of scars, although this embodiment is described in the specification. In view of this amendment and explanation, applicants respectfully request the Examiner to withdraw this rejection.

VI. Claim Rejections – 35 U.S.C. § 103

Claims 1-3, 6 and 12- 16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Barritault *et al.* (US 2001/0021758) ("Barritault") in view of Vergnolle *et al.* (TIPS, 2001) ("Vergnolle"). According to the Examiner, Barritault teaches the compounds of the invention have several different properties, including inhibition of protease activities that are implicated in the inflammatory process. The Examiner admits that Barritault does not teach the treatment of pain associated with a tissue, wherein the method does not treat the condition that causes the pain. Vernoglie is cited for teaching that all of the classical "hallmarks" (pain, swelling, redness, heat and impaired function) of inflammation have been observed following *in vivo* activation of PARS (protease-activated receptors) (p 147, col. 1, p 2). The Examiner concludes that it would have been obvious to a person of ordinary skill in the art at the time of the

invention to use the polymers of Barritault that inhibit protease activities implicated in the inflammatory process in a method of treating pain, wherein only the pain and not the underlying condition is treated. Applicants respectfully traverse this rejection.

Under US law, a *prima facie* case of obviousness is established if the teachings of the prior art would have suggested the claimed subject matter to a person of ordinary skill in the art. This is referred to as the "Teaching, Suggestion, Motivation" (TSM) test derived from *Graham v. John Deere*, 383 US 1 (1966). More recently, in *KSR Int'l Co. v. Teleflex Inc.*, 550 US 398, 127 S. Ct. 1727 (2007), the Supreme Court rejected the formalistic application of the TSM test. The Court held that under the facts before it, which involved a combination of known elements, the TSM test had been applied too rigidly. The Court said that the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. The present invention is in the pharmaceutical arts. Courts consider the pharmaceutical arts to be unpredictable. *See e.g., Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.* 520 F. 3d 1358 (Fed. Cir. 2008).

Here, the Examiner's position appears to be that because compounds within the scope of the invention have been shown to inhibit protease activities (paragraph [0067]) and that Vergnolle teaches the connection between pain, inflammation and protease-activated receptors (PARs), one of skill in the art would have found it obvious that the claimed compounds would treat pain by blocking the transmission of the pain from activated PAR2, without treating the underlying condition. In other words, the Examiner's argument assumes that all pain is caused by way of the same molecular pathway, that all protease inhibitors would be pain killers, and that all proteases would be inhibited by the polymers of the invention. Applicants argue that such reasoning ignores the unpredictability of the science and, more importantly, ignores examples within the cited art itself that undermine the Examiner's conclusion.

For instance, Barritault shows in Example 5 that the protease trypsin is not inhibited by the polymer (Figures 14 and 15) yet the same polymer does protect FGF and TGFbeta against trypsin degradation. And, protection against trypsin degradation is not demonstrated by all the disclosed polymers. In Figure 15, CM1DS2 is shown to provide FGF with 100% protection but provides TGFbeta with only 80% protection. These results highlight the unpredictability of the art of the invention.

Applicants also submit herewith Ledoux, D. *et al.*, "Human Plasmin Enzymatic Activity Is Inhibited by Chemically Modified Dextrans" *The J. of Biological Chemistry*, 275: 29383 (2000). Ledoux shows in Figure 3 that plasmin is or is not inhibited according to the polymer used. Figure 4 addresses the same question with trypsin and chymotrypsin, more general serine proteases (see page 29386). Yet, these same polymers belong to the same family as those described as pain killers, and are thus considered analgesic molecules. In the final paragraph at page 29390, right column, Ledoux *et al.* state that:

> In this study, we provide *in vitro* evidence that some dextran derivatives could contribute to the regulation of plasmin activity by impeding the plasmin generation, as a result of the binding to plasminogen and also by directly affecting the catalytic activity of the enzyme. Interestingly, only RG1192 retain an inhibitory capacity toward plasmin when tested under physiological ionic strength (K_i=3X10^{-7}M). Since RB1192 and RB1503 both present *in vivo* tissue repair activity, our data indicate that plasmin inhibition is not involved as a unique or key mechanism of action of these compounds. However, *due to the very high complexity and the numerous factors involved in tissue healing*, the use of various biopolymers with specific properties sucha s RG1192 and RG1503 may provide the tools required for the better understanding of wound healing property of these molecules. (emphasis added)

Applicants rely upon these teachings to highlight the complexity of the process by which protease inhibitors function and the unpredictable nature of related molecules. The polymers described in Ledoux *et al.* belong to the same family as those applicants have discovered to have analgesic properties. At the time of the invention, the properties of molecules similar to those described by applicants were not understood. Clearly, no link had been established between protease inhibition and analgesic properties. The Examiner's theory is based upon hindsight and the Examiner's

knowledge of applicants' invention. It is well known that not all pain killers are protease inhibitors and that all protease inhibitors are not pain killers. And, applicants have shown that not all proteases are inhibited by the polymers of the present invention. In view of the above teachings and explanations, and contrary to the Examiner's conclusions, at the time of the invention, one of skill in the art would not have found the claimed invention obvious.

Without conceding that the Examiner has set forth a *prima facie* case of obviousness, Applicants again draw the Examiner's attention to the comparative data in the present application. The degree to which the polymers of the invention treat pain was unexpected. Specifically, applicants direct the Examiner's attention to 24 Examples in the present specification describing the treatment of pain, caused by a wide variety of things, with the use of specific polymers. These Examples demonstrate that the biocompatible polymers of the present invention have a greater effect on pain when compared to the more powerful known analgesic, such as Diantalvique and/or morphine, regardless of what causes the pain (see for example, Example II of the specification). Moreover, the Examples clearly demonstrate that the treatment of pain using the polymers of the invention is faster than treatment with known compounds (see Example II of the specification). Applicants argue that the broad applicability and speed and efficacy of the invention would have been unexpected, and therefore, non-obvious over the prior art.

The Examiner also rejects claims 1-3, 6 and 12 under 35 USC § 103(a) as being obvious over Barritault and Vergnolle as applied to claims 1-3, 6 and 12-16 above, and further in view of Deibig (US 4,451,452) ("Deibig"). The Examiner states that "...Barritault and Vergnolle teach the treatment of pain without treatment of the cause of the pain, using polymers according to formula (1), because these polymers inhibit protease activities implicated in the inflammation process." The Examiner continues that "...the polymers may be substituted with various groups Z such as which are capable of conferring supplementary biological or physicochemical properties, such as better solubility or lipophilic properties enabling better diffusion or tissue penetration,

increasing amphophilic properties, such as amino acid, fatty acids fatty alcohols, ceramides or nucleotide addressing sequences (paragraph [0057])...." The Examiner admits that Barritault does not disclose polymers substituted with acetate groups as Z and Deibig is cited to compensate for this gap in teachings. According to the Examiner, Deibig discloses the modification of the carboxymethylated and O-sulphonated biocompatible polymers of Barritault with acetate groups. The Examiner concludes that the person of ordinary skill in the art would have been motivated to make those modifications to alter the swellability and solubility properties of the resulting polymers and reasonably would have expected success because Deibig disclose that substitution of dextran with carboxylic acids such as acetate affects the physical properties of the final polymers, allowing for polymers with a wide variety of final characteristics based on the identity and degree of substitution of the polymer.

Applicants traverse this rejection for reasons set forth above with regard to the Examiner's rejection over Barritault combined with Vergnolle. Deibig does not cure the deficiencies pointed out above. However, as applicants have previously pointed out, Deibig is deficient for other reasons. Deibig only discloses a polymer that can be used to support active molecules. It does not disclose or suggest that polymer AXY with a Z group as defined in the claims would have better properties. Moreover, the compounds disclosed in Deibig are different from those of the present invention and one could not have predicted that a same chemical group or substituent would have had the same effect. In view of the shortcomings of Deibig alone and in combination with Barritault and Vergnolle, applicants respectfully request the Examiner to withdraw this rejection.

CONCLUSION

In view of the above amendment and arguments, applicants believe this application is in condition for allowance. Should the Examiner believe that anything further is necessary in order to place this application in better condition for allowance, the Examiner is requested to contact the undersigned at the telephone number listed below.

Applicants believe no further fees are due with this response. In the event that additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefore are hereby authorized to be charged to our Deposit Account No. 01-2300 (referencing docket number 021305.00321) from which the undersigned is authorized to draw.

Dated: November 23, 2010

Respectfully submitted,

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